

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application n° PCT/FR2004/002687	International filing date (day/month/year) 20.10.2004	Priority date (day/month/year) 20.10.2003	
International Patent Classification (IPC) or both national classification and IPC C07K16/34, C07K16/00, A61K39/395			
Applicant : LABORATOIRE FRANCAIS DU FRACTIONNEMENT ...			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 11 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. <input checked="" type="checkbox"/> (sent to the applicant and to the International Bureau) a total of <u> 7 </u> sheets, as follows: <input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the report <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input checked="" type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application			
Date of submission of the demand of international preliminary examen 10.10.2005		Date of completion of this report: 20.12.2005	
Name and postal address of authority conducting international preliminary examination European patent office – P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk – Pays Bas Tel : +31 70 340 - 2040 Tx: 31 651 epo nl Fax : +31 70 340 - 3016		Authorized officer Le Flao, K Telephone n° : +31 70 340 - 1040	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application n°
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Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion is based on a translation from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1 (b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the elements* of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

the description, pages

1-35 as originally filed/furnished

the description part reserved to the sequence listing, pages

1-4 as originally filed/furnished

the claims, No.

1-40 received on 10.10.2005 accompanied by letter dated 04.10.2005

the drawings, sheets

1/9-9/9 as originally filed/furnished

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to the sequence listing (*specify*):
4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to the sequence listing (*specify*):

* If item 4 applies, some or all of those sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: 1-10

because:

☒ the said international application, or the said claims Nos. 1-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claim Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard.

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has, within the applicable time limit:
- ☐ restricted the claims
 - ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☒ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ neither restricted the claims nor paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:
- ☐ complied with
 - ☒ not complied with for the following reasons:

see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts
 - ☒ the parts relating to claims Nos. 1-28, 31-40 .

Box No. V Reasoned statement under Rule 35.2, with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes:	Claims	3-5, 11-28, 31-40
	No:	Claims	1, 2, 6-10
Inventive step	Yes:	Claims	
	No:	Claims	1-28, 31-40
Industrial applicability:	Yes:	Claims	1-28, 31-40
	No:	Claims	1-10

2. Citations and explanations (Rule 70.7) :

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Supplement Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing
 - ☒ contained in the international application as filed
 - ☒ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search and/or examination
 - ☐ received by this Authority as an amendment on
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY
(SEPARATE SHEET)**

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Regarding point III

The present Authority considers that the subject-matter of claims 1-10 is concerned by the provisions of Rule 67;1 (iv) PCT. On this account, no opinion will be given regarding whether or not the subject of these claims can be given industrial applicability (PCT article 34(4) a) i).

Regarding point IV

This Authority considers that the claims cover the three following inventions:

- i Claims 1-10 and 28 relate to the use of divalent or trivalent metal cations to improve the functional activity of antibodies.
- ii Claims 11-27 and 31-40 relate to the problem of providing a **modified antibody** having a fixation site for a divalent or trivalent metal cation.
- iii Claims 29 and 30 concern the use of zinc ions to **crystallize** antibodies.

The reasons for which the present application covers three inventions, unrelated to each other, so that they only form one general inventive concept, as required by PCT Rule 13.1, are the following:

Document WO9116912 (D1) describes the region adjacent to the variable domain which binds to the antigen of antibodies as being a region forming a binding site to a metal (p.2, l.14 – p.3, l.13). From D1 a QM212 antibody is known binding to zinc, cadmium and copper (Figures 1-4 and key p.4 - p.5). The use of divalent metal cations is therefore known from D1 to improve the functional activity of antibodies. Document XP002056577 (D2) describes the use of solutions containing zinc to improve the binding of antibodies to antigens in immunohistochemistry (see abstract of D2).

These documents describe different links between antibodies and divalent or trivalent metal cations: binding site outside the variable domain or improved binding to the antigen. The fact that divalent or trivalent metal cations can be associated with antibodies cannot therefore be the unique inventive concept linking the different inventions.

**WRITTEN OPINION OF THE INTERNATIONAL
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(SEPARATE SHEET)**

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Therefore, each solution represents a separate invention, characterized by its own technical characteristics.

In the present application, there does not seem to be any other special technical characteristic in the meaning of PCT Rule 13.2 which could form a unique inventive concept. That the binding of a cation to an antibody via the Fc fragment improves functional activity is a hypothesis which does not amount to a technical characteristic in the meaning of PCT Rule 13.2

The above analysis shows that neither the special technical elements of the invention groups nor the objective problems to be solved by these inventions are identical or show correspondence, and that no general inventive concept links the invention groups together. The present application does not therefore meet the conditions of unity of invention required by PCT Rules 13.1 and 13.2.

Regarding point V

INVENTION 1

Reference is made to the following documents:

- D1: WO 91/16912 A (Scripps Clinic and research Foundation) 14 November 1991.
- D2: BECKSTEAD JAY H: "A simple technique for preservation of fixation-sensitive antigens in paraffin-embedded tissues" (JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, vol.42, n°8, 1994, pages 1127 – 1134, XP002056577).
- D3: MINTZE KAREN *et al*: "Optimization of proliferating cell nuclear antigen (PCNA) immunohistochemical staining: A comparison of methods using three commercial antibodies, various fixation times, and antigen retrieval solution". JOURNAL OF HISTOTECHNOLOGY, vol. 18, n°1, 1995, pages 25-30, XP008032090.

NOVELTY

Document D1 describes the region adjacent to the variable domain which binds to the antigen of antibodies as being a region forming a binding site to a metal (p.2, l.14 – p.3, l.13).

From D1 a QM212 antibody is known binding to zinc, cadmium and copper (Figures 1-4) and key p.4 - p.5). The use of divalent metal cations is therefore known from D1 to improve the functional activity of antibodies since the term "to improve the functional activity of antibodies" is vague and general (see point VIII). Claims 1, 2 and 6-10 are therefore not novel with respect to D1. Claims 3-5 and 28 are novel.

INVENTIVE STEP

Claims 3-5 and 28 are novel but have no technical backing in the description (see point VIII below). They therefore form arbitrary solutions not involving an inventive step.

INDUSTRIAL APPLICABILITY

There does not exist any unified criterion among the PCT-contracting States to determine whether claims 1 - 10 can be given industrial applicability. Patentability may also depend on the manner in which the claims are formulated. Therefore the European Patent Office does not consider that industrial applicability can be given to the subject of claims for the use of a compound for medical purposes. On the other hand, claims may be accepted which relate to the first use of a known compound for medical purposes, and claims relating to the use of said compound to manufacture a medicinal product with a view to a new medical treatment.

INVENTION II

Reference is made to the following documents:

- D4: FIRAN MIHAIL *et al*: "The MHC class-1 related receptor, FcRn, plays an essential role in the maternofetal transfer of gamma-globulin in humans". INTERNATIONAL IMMUNOLOGY, vol. 13, n°.8, August 2001, pages 993-1002. XP002333400.
- D5: JEFFERIS R *et al*: "IgG-Fc-mediated effector functions: molecular definition of interaction sites for effector ligands and the role of glycosylation". IMMUNOLOGICAL REVIEWS, vol. 163, June 1998, pages 59-76, XP001203450.
- D6: WO 01/77181 A1 (Glacet Arnaud *et al*), 18 October 2001.

NOVELTY

Claims 11-19 are novel since they relate to a IgG3-type antibody. Claims 20-27 are novel and differ from D6 in that the metal cation content is at least equal to the antibody content. Claims 31-40 are novel since they concern an antibody having modified His 310 and His 435 residues.

INVENTIVE STEP

The subject of claim 11 differs from the disclosure in D4, considered as the closest state of the art, in that it concerns an antibody of class IgG3 containing the His 310 and His 435 residues on its Fc region created by molecular engineering. The hypothesis which leads to the experiments described in examples 3 and 4 is the following: the His 310 and His 435 residues play an essential role in the binding of the zinc cation to the CH2-CH3 interface of IgG1s (p.27, l.13 - l.16). The mutagenesis experiments were conducted with the EMAB5 antibody (p.27, l.22), which is a IgG1-type antibody. It is therefore considered that no technical effect associated with the difference has been shown in the present application. Therefore the claimed solution does not solve the technical problem of providing an antibody of class IgG3 having a fixation site for a metal cation on its Fc region created by molecular engineering. Claim 11 does not therefore involve an inventive step. The same reasoning applies to claims 12-19.

Claims 20-27 are not inventive with respect to D6 which describes the R297 antibody, an anti-Rhesus D IgG1-type antibody produced in the same cell line as EMAB5 (YB2/0) and having the same properties as EMAB5. That R297 has the His 310 and His 435 residues is considered to be an implicit technical characteristic since they are the usual residues of an IgG1. No particular effect is associated with the difference and these claims therefore form arbitrary solutions which do not involve an inventive step.

The subject of claim 35 differs from D4, which describes a humanised IgG1-type antibody comprising the H435A mutation which no longer binds to the FcRn receptor, in that it concerns an antibody whose His 310 and His 435 residues are substituted by lysine residues, whereas D4 describes the His 310 Ala substitution (D4, summary and p.996: H310A). No particular effect is associated with the difference since the mutated antibody described in D4 does not bind to the FcRn receptor, which shows that the H310 residue alone is essential for binding to the receptor. The technical problem is therefore to provide an

alternative antibody deprived of the binding capacity to the Fc gamma receptor. The proposed solution is considered to be an arbitrary choice, which does not involve an inventive step.

Regarding point VIII

The examples in the description refer to the anti-Rhesus D EMAB5 antibody (p.19 to p.32). It is considered that the name EMB5 is an internal designation. Document D6 describes an equivalent antibody called R297 (which is also an internal designation). If the antibody has been deposited with an approved depositing authority, it would be preferably to use a reference derived from the official designation such as it is published in the order number of the deposited biological material in order to avoid the use of internal designations.

INVENTION 1

Claims 1-7 which concern the use of metal cations to improve the functional activity of antibodies do not meet the conditions required by PCT Article 6, insofar as the subject-matter for which protection is sought is neither clearly defined nor supported by the description.

Firstly the use of the term "to improve the functional activity of antibodies" in claim 1 defines this object through the result to be achieved, which merely amounts to stating the fundamental problem which the invention sets out to solve, without providing the necessary technical characteristics to achieve this result.

Secondly, claim 1, relating to a medical indication since it does not contain the "*in vitro*" limitation, is not admissible under PCT Article 6. Therapeutic use is defined functionally by a mechanism of action which does not allow practical application in the form of a true, well-defined treatment for a pathological condition (disease) (C-IV, 4.2). Since in addition the medical use has no support in the description, the objection can only be circumscribed by limiting claim 1 to *in vitro* use. This last remark also applies to claim 8.

The subject of independent claims 1, 8 and 28 is not supported by the description since it is not shown either that the divalent or trivalent metal cations improve the functional activity of antibodies or that the solutions according to claim 28 are of particular interest.

**WRITTEN OPINION OF THE INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY
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INVENTION II

The subject of claims 11-27 which relates to type-IgG3 antibodies, and the subject of claims 39 and 40 have no technical support in the description whose examples relate to an anti-Rhesus D IgG1-type antibody (EMAB5 in the examples, also called R297 in D6), which is contrary to Article 6 PCT.

APR 20 2006
LAP 20 REC'D PCT/PTO 20 APR 2006CLAIMS

1. Use of divalent or trivalent metallic cations to improve the functional activity of antibodies, said functional activity being ADCC activity (Antibody-Dependent Cell-mediated Cytotoxicity), CDC activity (Complement Dependent Cytotoxicity), phagocytosis activity, endocytosis activity or the induction of cytokine secretion.

2. Use of claim 1, characterized in that said antibodies are human IgGs or having a human Fc region.

3. Use of claim 1 or 2, characterized in that said cations interact with the Fc region of said antibodies.

4. Use of anyone of claims 1 to 3, characterized in that said cations take part in controlling the opening of the Fc region of said antibodies.

5. Use of anyone of claims 1 to 4, characterized in that said cations promote fixing of said antibodies to the FcγR receptors, in particular the FcγRIII receptor.

6. Use of anyone of claims 1 to 5, characterized in that said cation is zinc, iron, copper or cadmium.

7. Use of anyone of claims 1 to 6, characterized in that said cation is zinc.

8. Method for potentialising the functional activity of antibodies, said functional activity being ADCC activity (Antibody-Dependent Cell-mediated Cytotoxicity), CDC activity (Complement Dependent Cytotoxicity), phagocytosis activity, endocytosis activity or the induction of cytokine secretion, comprising a step consisting of adding a suitable quantity of at least one divalent or trivalent metallic cation to the biological system producing the antibodies or to a solution

comprising antibodies before and/or after purification, or to the storage solution, or to the end formulation in the form of an injectable solution of antibodies.

5 9. Method of claim 8, characterized in that said cation is zinc, iron, copper or cadmium.

10 10. Method of claim 9, characterized in that a zinc molar concentration is added at least equal to the molar concentration of antibody.

15 11. Class IgG3 antibody having a fixing site for a divalent or trivalent metallic cation comprising the His 310 and His 435 residues (Kabat numbering) on its Fc site created by molecular engineering.

20 12. Antibody of claim 11, characterized in that said fixing site comprises the Asn 434 residue and/or the His 433 residue (Kabat numbering).

25 13. Antibody of claim 11 or 12, characterized in that said fixing site is created by substitution of Arg 435 by His 435.

30 14. Antibody of claim 11 or 12, characterized in that at least one of said histidine residues is replaced by at least one of the residues chosen from among cysteine, aspartic acid and glutamic acid.

35 15. Antibody of anyone of claims 11 to 14, characterized in that it has a divalent or trivalent metallic cation fixed onto said fixing site.

 16. Antibody of anyone of claims 11 to 15, characterized in that said cation is zinc, iron, copper or cadmium.

17. Antibody of anyone of claims 11 to 16, characterized in that the allotype of said antibody is G3m(b) or G3m(g).

18. Antibody of anyone of claims 11 to 17, characterized
 5 in that it has improved fixing to FcγRIII and improved functional activity with respect to the native antibody, said functional activity being ADCC activity (Antibody-Dependent Cell-mediated Cytotoxicity), CDC activity (Complement
 10 activity or the induction capacity of cytokine secretion.

19. Use of the antibody of anyone of claims 11 to 18, for the preparation of a medicinal product to treat pathologies such as haemolytic disease of the newborn, a
 15 viral, bacterial or parasitic pathology, a pathology related to pathogenic agents or derived toxins, listed as being particularly dangerous in the event of bioterrorism (classification of the Centers for Disease Control, CDC), in particular anthrax (*Bacillus anthracis*), botulism (*Clostridium*
 20 *botulinum*), the plague (*Yersinia pestis*), smallpox (*Variola major*), tularaemia (*Francisella tularensis*), viral haemorrhagic fevers (related to filoviruses: Ebola, Marburg and to arenaviruses - Lassa, Machupo), the epsilon toxin of *Clostridium perfringens*, brucellosis (*Brucella species*),
 25 melioidosis (*Burkholderia mallei*) the toxin of castorbean (*Ricinus communis*).

20. Pharmaceutical composition of therapeutic antibodies comprising divalent or trivalent metallic cations whose
 30 content is at least equal to the antibody content, and at least one excipient.

21. Composition of claim 20, characterized in that said antibodies have a divalent or trivalent metallic cation on the
 35 His 310 and His 435 residues (Kabat numbering).

22. Pharmaceutical composition of claim 20 or 21, characterized in that said antibodies are the antibodies of claims 11 to 18 or human IgGs or having a human Fc region.

5 23. Pharmaceutical composition of anyone of claims 20 to 22, characterized in that the metallic cations are zinc, iron, copper or cadmium, or a mixture of several of these.

10 24. Pharmaceutical composition of claim 23, characterized in that said cation is zinc, in particular zinc acetate, zinc bromide, zinc citrate, zinc hydroxycarbonate, zinc iodide, zinc L-lactate, zinc nitrate, zinc stearate, zinc gluconate, zinc sulphate, zinc chloride or zinc hydrochloride.

15 25. Pharmaceutical composition in which at least 50%, 60%, 70%, 80%, 90% or even 99% of the antibodies have a bound divalent or trivalent metallic cation, in particular bound to the site comprising the His 310 and His 435 residues (Kabat numbering).

20 26. Composition of claim 25, characterized in that said site comprises the His 433 and/or Asn 434 residues (Kabat numbering).

25 27. Composition of claim 25 or 26, characterized in that said metallic cation is zinc, iron, copper or cadmium or a mixture of several of these.

30 28. Solution comprising a monoclonal antibody or polyclonal antibodies and a suitable quantity of divalent or trivalent metallic cation, in particular a zinc ion concentration at least equal to the antibody concentration, said solution being adapted for injection via intravenous, intramuscular or subcutaneous route.

35 29. Use of zinc ions to improve the crystallisation of therapeutic antibodies.

30. Test which can be used to assess the efficacy of an antibody, comprising study of the 3D conformation of the domain involving His 310, His 435, His 433 and/or Asn 434 (Kabat numbering) such as shown in figure 1 or 2, or an assay of the zinc content of said antibodies, the presence of zinc being an indication of the efficacy of the antibody.

31. Antibody having modification of at least one of its His 310 and His 435 residues (Kabat numbering).

32. Antibody of claim 31, characterized in that said modification is a mutation.

33. Antibody of claim 32, characterized in that said mutation is a substitution by an amino acid having a low affinity for said metallic cations.

34. Antibody of claim 33, characterized in that said amino acid is lysine, alanine, glycine, valine, leucine, isoleucine, proline, methionine, tryptophan, phenylalanine, serine or threonine.

35. Antibody of anyone of claims 32 to 34, characterized in that the His 310 and His 435 residues are substituted by lysine residues.

36. Antibody of claim 31, characterized in that the modification is made by DEPC.

37. Antibodies of anyone of claims 31 to 36, characterized in that they belong to the IgG1 sub-class.

38. Antibodies of anyone of claims 31 to 37, characterized in that they have reduced functional activity with respect to the same non-modified antibody, said functional activity being ADCC activity (Antibody-Dependent

Cell-mediated Cytotoxicity), CDC activity (Complement Dependent Cytotoxicity), phagocytosis activity, endocytosis activity or the induction capacity of cytokine secretion.

- 5 39. Use of anyone of antibodies 31 to 38 to prepare a medicinal product intended to prevent graft rejection or for the treatment of a pathology chosen from among tetanus, diphtheria, or caused by a pathogenic agent or derived toxin, listed as being particularly dangerous in the event of
- 10 bioterrorism (classification of the Centers for Disease Control, CDC), in particular anthrax (*Bacillus anthracis*), botulism (*Clostridium botulium*), the plague (*Yersinia pestis*), smallpox (*Variola major*), tularaemia (*Francisella tularensis*), viral haemorrhagic fevers (related to filoviruses: Ebola,
- 15 Marburg and to arenaviruses - Lassa, Machupo), the epsilon toxin of *Clostridium perfringens*, brucellosis (*Brucella species*), melioidosis (*Burkholderia mallei*) the toxin of castorbean (*Ricinus communis*).

- 20 40. Use of the antibody of anyone of claims 31 to 38 for the preparation of a medicinal product to replace IgG4s.